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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,126	03/14/2001	Torben Halkier	3631-0108P	6308

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,126	HALKIER ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 28* is/are pending in the application.

4a) Of the above claim(s) *25-27 and 29-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 28* is/are rejected.

7)☒ Claim(s) *1-24 and 28* is/are objected to.

8)☒ Claim(s) *1-56* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (Claims 1-24 and 28) drawn to a method for *in vivo* down-regulation of osteoprotegerin ligand (OPGL) activity in an animal comprising administration of human OPGL (SEQ ID NO: 2) and the truncated human OPGL (residues 159-317) where residues 257-262 are substituted with an inserted P2 epitope (SEQ ID NO: 34) in Paper No. 11 (12 August 2002) is acknowledged. The traversal is on the ground(s) that the Examiner has improperly applied the PCT unity of invention guidelines. This is not found persuasive because this application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. The special technical feature of Group I is a method for *in vivo* down regulation of osteoprotegerin ligand activity in an animal comprising administering protein. The special technical feature of Group II is a method for *in vivo* down regulation of osteoprotegerin ligand activity in an animal comprising administering nucleic acid. The special technical feature of Group III is a method for treating osteoporosis comprising administering a protein. The special technical feature of Group IV is a method for treating osteoporosis comprising administering nucleic acid. The special technical feature of Group V is the OPGL analogue. The special technical feature of Group VI is the nucleic acid, vector, cell, and method of preparing the cell. The special technical feature of Group VII is a method for *in vivo* down regulation of osteoprotegerin ligand activity in an animal comprising administering transformed cells or viruses. The special technical feature of Group VIII is a pharmaceutical composition comprising nucleic acid. The special technical feature of Group IX is a method of identifying OPGL polypeptides. The special technical feature of Group

X is a method of identifying OPGL nucleotides. The special technical feature of Group XI is the use of OPGL and an adjuvant. The special technical feature of Group XII is the use of OPGL analogue and an adjuvant. The inventions listed, as Groups do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons. Groups I, II, III, IV, VII, IX, and X are directed to methods which recite structurally and functionally distinct elements which are not required one for the other and/or achieve different goral and thus do not share a common special technical feature. The products of Groups V, VI, VIII, XI, and XII are directed to different products, which do not share a common special technical feature. The products are distinct both physically and functionally, are not required one for the other, can be prepared by processes which are materially different, isolated from diverse sources and/or used in different methods. Finally, each Group would require a separate and distinct search presenting an undue search burden on the examiner. Therefore, restriction was required under 35 U.S.C. 121 and 372.

2. Claims 25-27 and 29-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 1-24 and 28 will be examined to the extent that they read on a method for *in vivo* down-regulation of osteoprotegerin ligand (OPGL) activity in an animal comprising administration of human OPGL (SEQ ID NO: 2) and the truncated human OPGL (residues 159-317) where residues 257-262 are substituted with an inserted P2 epitope (SEQ ID NO: 34).

Status of Application, Amendments, and/or Claims

3. Claims 25-27 and 29-56 are withdrawn from consideration as discussed above and claims 1-24 and 28 are under examination.

4. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Information Disclosure Statement

5. The information disclosure statement filed 14 March 2001 (Paper No. 5) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Fuller et al. (1998) is not present with the application. The information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1). Applicant is invited to submit a replacement Fuller et al. (1998) citation identical to the information disclosure statement filed 14 March 2001 (Paper No. 5) with the response to this office action for no additional fee.

Claim Objections

6. Claims 1-24 and 28 are objected to because of the following informalities: specifically recite non-elected inventions. Appropriate correction is required.

7. Claims 8-14, 16-24, and 28 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 8-24, and 28 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-24 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 1 is directed a method for *in vivo* down-regulation of osteoprotegerin ligand (OPGL) activity in an animal comprising administration of a peptide. Claim 2 is directed to the method of claim 1 wherein an OPGL analogue with at least one modification of the OPGL amino acid sequence is presented. Claim 3 is directed to the method according to claim 2, wherein the modification has a result that substantial fraction of OPGL B-cell epitopes are preserved. Claim 4 is directed to the method according to claim 3 wherein the modification includes introduction as side groups, by covalent or non-covalent binding to suitable chemical groups in OPGL or a subsequence thereof. Claim 5 is directed to the method according to claim 3 or 4, wherein the

modification includes amino acid substitution and/or deletion and/or insertion and/or addition. Claim 6 is directed to the method according to claim 5, wherein the modification results in the provision of a fusion polypeptide. Claim 7 is directed to the method according to claim 5 or 6, wherein introduction of the amino acid change results in a substantial preservation of the overall tertiary structure of OPGL. Claim 8 is directed to the claimed method wherein the modification includes duplication of at least one OPGL B-cell epitope and/or introduction of a hapten. Claim 9 is directed. Claim 9 is directed to the claimed method wherein the foreign T-cell epitope is immunodominant in the animal. Claim 10 is directed to the claimed method wherein the foreign T-cell epitope is capable of binding to a large proportion of MHC Class II molecules. Claim 11 is directed to the method according to claim 10, wherein at least one foreign T-cell epitope is selected form a natural T-cell epitope and an artificial MHC-II binding peptide sequence. Claim 12 is directed to the method according to claim 11, wherein the natural T-cell epitope is SEQ ID NO: 34. Claim 15 is directed to the method according to claim 6, describing the cytokines. Claim 18 is directed to the method according to claim 17, wherein the modification comprises a substitution. Claim 19 is directed to the method according to claim 18, describing the amino acid sequence changes containing the foreign TH epitope substitutes amino acid stretches. Claim 23 is directed to the method according to claim 22, detailing the effective amount administered. Claim 24 is directed to the method according to claim 22 or 23, wherein the OPGL polypeptide or analogue is contained in a virtual lymph node (VLN) device. Claim 28 is directed to the claimed method wherein at least one administrations/introductions per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations/introductions.

9. The specification teaches that osteoprotegerin ligand (OPGL) is a novel member of the tumor necrosis factor family of cytokines that exists in both a membrane-bound and a soluble form. OPGL binds to osteoprotegerin with a binding affinity of 4 nM. *In vitro*, OPGL activates mature osteoclasts and modulates osteoclasts formation from bone marrow precursors in the presence of CSF-1. It has also been demonstrated that OPGL binds to the surface of osteoclasts progenitors in CSF-1-treated bone marrow. Recombinant soluble OPGL is a potent inducer of bone resorption *in vivo* and activates mature osteoclasts to resorb bone. To date, OPGL has not been observed to act as an osteoclasts growth factor or osteoclasts survival factor.

10. The art teaches that in bone, OPGL stimulates osteoclasts differentiation, enhances the activity of mature osteoclasts, and inhibits osteoclasts apoptosis: the net effect of these actions is to expand the pool of activated osteoclasts. In addition to effects on bone and mineral metabolism, OPGL has a variety of effects on T-cells and dendritic cell function (Hofbauer et al., 2000).

11. Thus the claimed invention is directed to a method for *in vivo* down-regulation of osteoprotegerin ligand (OPGL) activity in an animal comprising administration of a peptide, which is not supported by the teachings of the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specific biological actions/activities that the immunogenic peptide would effect; How do the antibodies effect OPGL; Expectation of antibodies to interfere with osteoclasts; The absence of working examples of the claimed invention. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by

the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

12. Regarding modification, the art recognizes that modification entails several chemical reactions, including but not limited to addition of chemical entities, removal of chemical entities, genetic mutations, and has unpredictable effects on a cell signaling molecule function. Due to the large quantity of experimentation necessary to all the applicable kinds of modification, the lack of direction/guidance presented in the specification regarding evaluating effects modification of the molecule, the absence of working examples directed to modified molecules, the complex nature of the invention, the unpredictability of the effects of modification on the function of molecules (WO 98/46751), and the breadth of the claims which fail to recite limitations for what constitutes modification, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

13. Regarding regulation, the art recognizes that regulation entails several steps, including but not limited to transcriptional, translation, post-translation modification, recognition, and inhibition (competitive, non-competitive, uncompetitive) and has unpredictable effects on a cell signal function. Due to the large quantity of experimentation necessary to all the applicable kinds of regulation, the lack of direction/guidance presented in the specification regarding evaluating effects of the claimed invention on regulation, the absence of working examples directed to down regulation, the complex nature of the invention, the unpredictability of the effects of regulation on function (Greenfield et al., 1999; Burgess et al., 1999; Lacey et a., 1998; Marks, 1989), and the breadth of the claims which fail to recite limitations for what constitutes

regulation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Regarding analogs, the art recognizes that even minor alterations to protein structure have unpredictable effects on a proteins function, in addition, analogue can pertain to chemical entities and biologically derived substances as well as proteinaceous substances. Due to the large quantity of experimentation necessary to all the applicable analogs of SEQ ID NO: 2 (and specified changes contained in the specification), the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating non-peptide analogs of SEQ ID NO: 2, the absence of working examples directed to non-peptide analogs of SEQ ID NO: 2, the complex nature of the invention, the unpredictability of the effects of mutation on protein structure and function (WO 98/46751), and the breadth of the claims which fail to recite limitations for what constitutes an analog, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Regarding amino acid substitution, the art recognizes that changing a codon which codes for a particular amino acid includes substitution, deletion, insertion, addition which can result in frame-shift mutations, single amino acid mutations, non-sense mutations, and silent mutations. Due to the large quantity of experimentation necessary to evaluate all the possible effects of mutation on peptide formation, the lack of direction/guidance presented in the specification on what specific mutations in the codons are to be acted upon, the absence of working examples directed to the effects of all the claimed mutations on the peptide, the complex nature of the invention, the unpredictability of the effects of mutations (Wells, 1990; Murray et al., 1990; Marks, 1989), and the breadth of the claims which fail to recite limitations for what effects

mutations would have on peptide formation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

16. Finally, the application must establish a nexus between the immunogenic modified peptide administered to the animal as recited in the claims and production of specific and effective self anti-OPGL antibodies that down regulate osteoprotegerin as recited in the claims. In this case, the skilled artisan is not guided as to how an antibody must affect one or more steps of the peptide activity such that the antibody would be determined to be one that down regulates osteoprotegerin. Also, regulation of osteoprotegerin involves several steps (Simonet et al., 1997; Bucay et al., 1998; Marks, 1989) and it is not clear that an anti-OPGL antibody is involved in a rate-limiting step for any of the various regulation steps such that it could be used down regulate osteoprotegerin.

17. Claims 1-7, 11-12, 15, 18-19, 23, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The method steps do not indicate how the anti-OPGL antibody must affect osteoprotegerin in order for the anti-OPGL antibody to be labeled a "down regulator" as recited in preambles. Thus the claims are incomplete.

18. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 15 recites the limitation "cytokine" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

19. Claims 1, 22, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Regarding claim 1, the phrase "including" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

21. Regarding claims 22 and 28, the phrase "such as" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Summary

22. Claims 1-24 and 28 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
October 30th, 2002

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER